EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900752

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900752

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COMMUNICATION

Synthesis of Carbon-branched Sugars Involving an Unprecedented 1,5- or 1,6-Alkyl Transposition Reaction

Perali Ramu Sridhar,* Boddu Umamaheswara Rao and Gadi Madhusudhan Reddy

Dedicated to Professor S. Chandrasekaran on the occasion of his 75th birthday

Abstract: An unusual 1,5- or 1,6-alkyl transposition along with acetalization of 3-deoxy glycals is reported. TMSOTf was used as the Lewis acid for carrying out the transformation. A plausible mechanism is proposed. The novel method provided an access to the synthesis of 2-*C*-branched bicyclic acetals of various deoxy-sugar derivatives as well as 2-*C*-branched levoglycosan derivatives.

Introduction

The structural reorganizational "shifts" in carbocation intermediates has received immense importance in the development of novel methodologies and innovative protocols for the total synthesis of several natural products.[1] The study of such intermediates form the basis of fundamental and practical chemistry.[2] A couple of named reactions have evolved based on the skeletal reorganization of this reactive species.[3] In this context, the oxocarbenium ion rearrangement reactions in carbohydrate derivatives have been immensely studied for a long time.[4] By virtue of the presence of the *endo*cyclic oxygen in these substrates stabilize the carbocation at the anomeric position by forming the oxocarbenium ion.[5] Glycals, the 1,2-unsaturated cyclic sugar derivatives, have been one of the primary sources for the generation of oxocarbenium ion, in the presence of an acid catalyst, to study various glycosylation reactions.[6] Appropriately functionalized glycals undergo rearrangement reactions in the presence of a Lewis acid catalyst.[7] Apart from the Ferrier type rearrangement of glycals, dimerization of glycals[8] and Gin's[9] hypervalent iodine mediated oxidative ring contraction of 6-deoxy-gulal are noteworthy. Steel *et al*. showed that 3,4,6-tri-*O*-benzyl D-glucal **1** in the presence of catalytic amount of acetyl perchlorate converts into a bicyclic acetal **3** through an unusual 1,7-hydrogen shift.[10] While carrying out this transformation using 3-deoxy 4,6-di-*O*-benzyl glycal **2** we have observed a stereoselective dimerization reaction which led to the formation of 2-(β-*C*-glycosyl)-glycal **4**[11] (Scheme 1). This typical reactivity of 3-deoxy glycals under Lewis acid conditions prompted us to investigate further on the fate of oxocarbenium ion generated using these scaffolds. Thus, herein, we report an unusual 1,6 or 1,5 alkyl transposition reaction of 3-deoxy glycals providing carbon branched 1,6-anhydrosugar derivatives.

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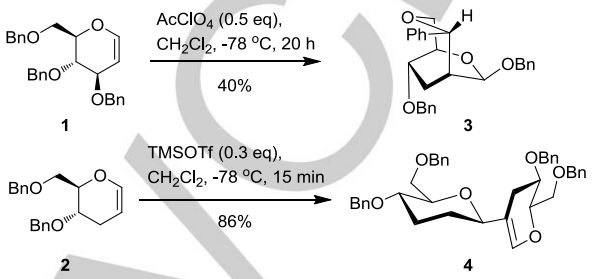
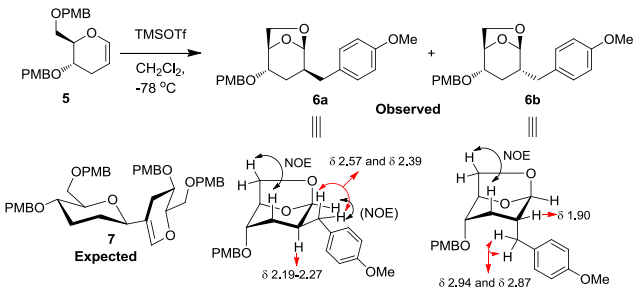


Scheme 1. Lewis acid catalysed 1,7-hydrogen shift and glycal dimerization reactions.

Results and Discussion

To study the influence of the protecting groups in the *C*-disaccharide formation using 3-deoxy glycals, we have attempted to carry out the dimerization reaction of 3-deoxy 4,6-di-*O*-(*p*-methoxybenzyl) glucal **5**. However, to our surprise, glycal **5** upon treatment with TMSOTf (0.1 eq) at -78 °C in dichloromethane did not provide the expected dimer **7**. Instead, the major product was found to be the 1,6-anhydro 2-*C*-branched levoglucosan derivatives **6a** and **6b**. The structure and stereochemistry of the products were fully established by ^{1}H, ^{13}C, COSY and NOESY NMR experiments (Scheme 2). In the proton NMR spectra of **6a,** the axial hydrogen at C2 position appeared as a multiplet at δ2.19-2.27 whereas in compound **6b** the equatorial hydrogen at C2 appeared at δ1.90. The difference in chemical shift value is apparent due to the 1,3-diaxial interactions between the axial oxygen at C4 which deshields the C2 axial hydrogen to a lower δ value in **6a**. Similarly, the protons on the benzyl carbon at C2 in compound **6a** appeared δ 2.39 and δ 2.57 whereas in **6b** they appear at δ 2.87 and δ 2.94. These chemical shift values again provide an ample evidence for the assigned stereochemistry at the C2 position for compound **6a** and **6b** (Scheme 2).



Scheme 2. An unprecedented 1,6-alkyl shift in 3-deoxy glucal derivative.

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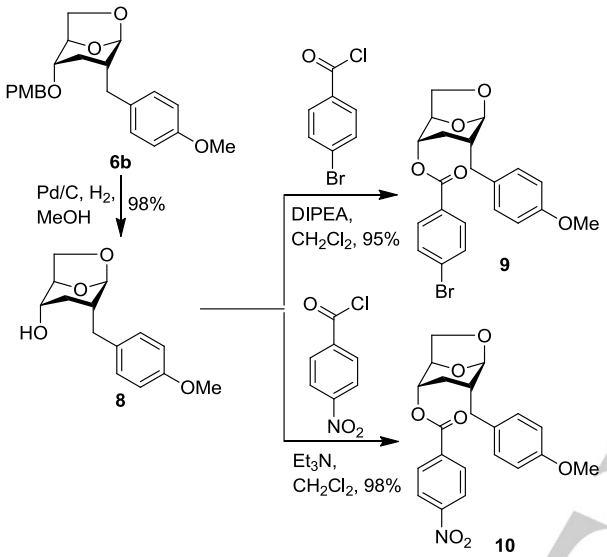
However, in view of obtaining the crystal structure, various methods to crystalize either compound **6a** or **6b** were unsuccessful. Then, we planned to synthesize derivatives of the compounds **6a** or **6b** expecting to get a crystal. Towards this, compound **6b** was subjected to the hydrogenolysis to get alcohol **8** which was esterified with 4-bromobenzoyl chloride and 4-nitrobenzoyl chloride to give the benzoate derivatives **9** and **10**, respectively (Scheme 3). To our fortune, compound **9** was found to be a solid and we were able to crystalize this using ethyl acetate and hexane. The ORTEP diagram of ester **9** is provided in the figure 1.[12]



Scheme 3. Synthesis of the derivatives of compound **6b**.

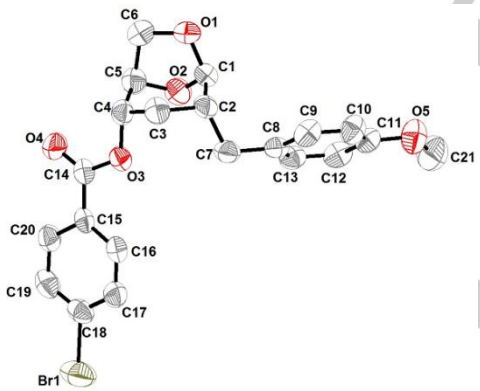
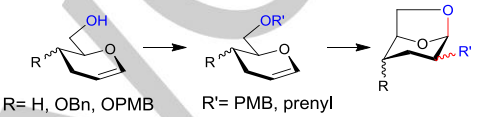
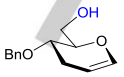
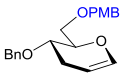
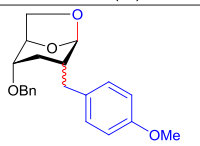
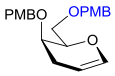
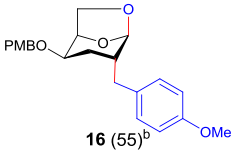
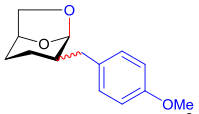
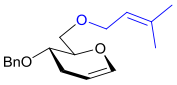
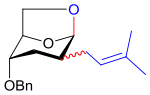
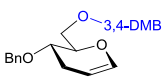
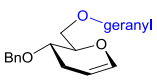
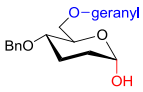
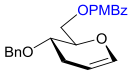
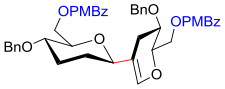


Figure 1. The ORTEP diagram of compound **9**.[12]

The unprecedented formation of the C2-branched bicyclic acetals **6a** and **6b** and the importance of levoglucosan (1,6-anhydrosugar) derivatives in the total synthesis of natural products[13] made us curious to study the generality of various orthogonally protected 3-deoxy glycal derivatives. Thus, 3-deoxy 4-*O*-benzyl 6-*O*-(*p*-methoxybenzyl) glucal **12**[14] was synthesized from 3-deoxy 4-*O*-benzyl glucal **11**[15] and subjected to TMSOTf (0.1 eq) at -78 °C. Interestingly, this reaction also provided the 2-*C*-branched levoglucosans **13a** and **13b**, as 1:1 mixture of diastereomers and no isolable amount of the corresponding 2-(β-*C*-glycosyl)-glycal derivative was observed. Application of the similar method on 3-deoxygalactal derivative **15**, synthesized from **14**, provided the corresponding 1,6-anhydro 2-(*p*-methoxybenzyl) 3-deoxy galactose derivative **16** as a single diastereomer in moderate yield (Table 1, entry 2). Interestingly, 6-*O*-(*p*-methoxybenzyl)-3,4-dideoxy glucal **18**,[16] obtained by the *p*-methoxybenzylation of **17**,[17] upon treating with TMSOTf provided a 1:1 diastereomeric mixture of 2-*C*-branched levoglucosan derivatives **19a** and **19b** via an unprecedented 1,6-migration of the *p*-methoxybenzyl (PMB) group.

Table 1. Synthesis of 2-*C*-branched levoglycosan derivatives by 1,6-alkyl transposition.



Entry	3-Deoxy glycal	Fully protected 3-deoxyglycals (%)[a]	6,8-Dioxabicyclo[3.2.1] octane (%)[a]
1	 **11**	 **12** (95)	 **13a:13b** (90) (1:1 mix)[b]
2	 **14**	 **15** (98)	 **16** (55)[b]
3	 **17**	 **18** (95)	 **19a:19b** (60) (1:1 mix)[c]
4	**11**	 **20**(80)	 **21a:21b** (50) (1:1 mix)[b,c]
5	**11**	 **22**(80)	 **23** (50)
6	**11**	 **24**(90)	 **25** (52)[c]
7	**11**	 **26** (85)	 **27** (51)[d]

[a] Yield refers to pure and isolated products. [b] The major byproduct was found to be the corresponding 2-(4-alkyloxy)6,8-dioxabicyclo[3.2.1]octane derivative. [c] The diastereomeric ratio was calculated based on the ^{1}H NMR spectra of crude product. [d] The stereochemistry at the anomeric position was assigned based on ^{1}H-^{1}H NOESY experiment.

We assumed that the possible reason for the migration of the PMB group from C6-oxygen to the C2 might be due to its higher carbocation stabilization than the unsubstituted benzyl group. Keeping this in mind, we further investigated the alkyl groups which could stabilize the carbocation. In this process, we have chosen to use the prenyl group in place of PMB. Thus, prenylation of glucal **11** provided the 3-deoxy 6-*O*-prenyl glucal derivative **20**, and it was subjected to the acid catalyzed 1,6-migration reaction. To our delight, under the similar reaction conditions, prenyl group underwent the 1,6-migration and provided the 2-*C*-prenyl levoglucosan derivatives **21a** and **21b** in 50% yield. To evaluate the feasibility of dimethoxy substituted benzyl migration the C-6 position of the glycal **11** was alkylated with 3,4-dimethoxy benzyl bromide to give compound **22** and subjected to catalytic TMSOTf at -78 °C. However, this reaction did not yield the expected 2-*C*-branched glycal. Instead, the reaction provided only the 2,3-dideoxy levoglucosan derivative **23**. Later, a C-6 geranylated glycal **24** was synthesized and subjected to the migration reaction conditions. Surprisingly, it was found that the geranyl group was very stable under the reaction conditions and no reaction was observed at -78 °C. When the reaction mixture was warm to 0 °C, hydration of the glycal was observed and the product **25** was isolated in 52% yield. These results suggest that only some typical carbocation stabilizing groups could be allowed to this novel unprecedented migration reaction. Further, to investigate the migratory aptitude of the *p*-methoxybenzoyl group, 3-deoxy 4-*O*-benzyl 6-*O*-benzoyl glucal **26** was synthesized by *p*-methoxybenzoylation of **11**, and subjected to TMSOTf. However, the reaction provided the 2-(β-*C*-glycosyl)-glycal derivative **27** as the only isolable product in 51% yield (Table 1, entry 7).

Based on the product formation, a possible mechanism is proposed for the formation of the 2-*C*-branched levoglucosan derivative. Accordingly, glycal **5** upon reaction with TMSOTf might form the corresponding oxo-carbenium ion intermediate **5a**. This oxocarbenium ion can further undergo deprotonation to give the 2-trimethylsilyl glycal derivative **5b** and triflic acid. On the other hand, intermediate **5a** can have the resonance structure **5c** by the

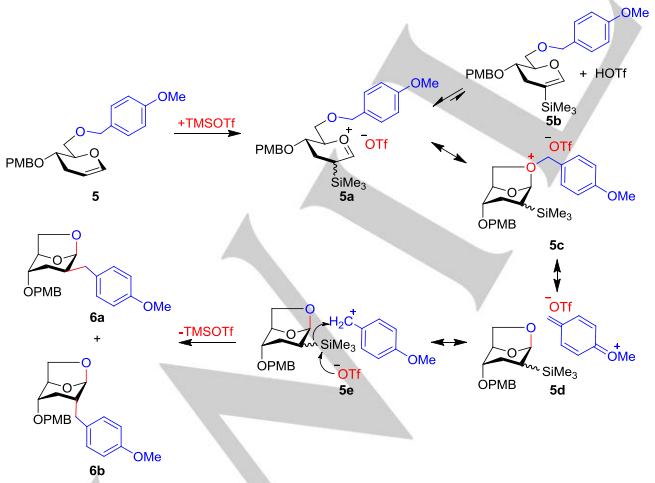
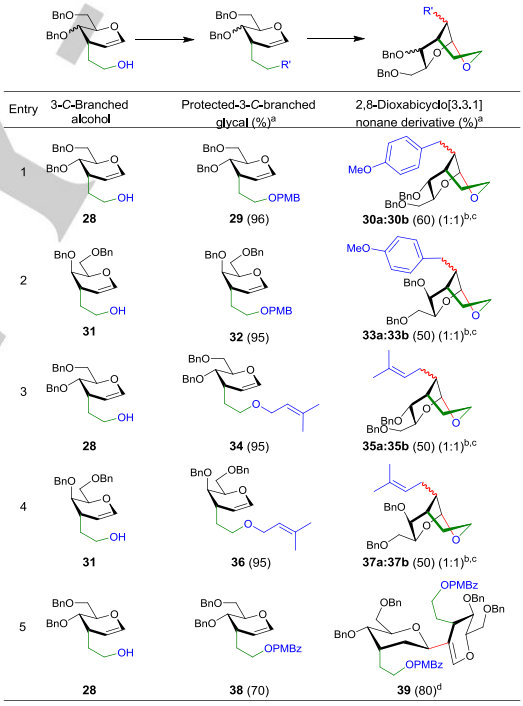


Figure 2. Proposed mechanism for the 1,6-alkyl transposition reaction; Synthesis of 2-*C*-branched levoglycosan derivatives.

Participation of the lone pair of electrons present on the C6-oxygen which further will have the extended resonance structures **5d**[18] and **5e**. Finally, regeneration of the catalyst, TMSOTf, by reaction of the triflate anion on to the trimethylsilyl group which could help in the formation of a new C-C bond between C2 and the *p*-methoxybenzyl carbon will lead to the formation of the 1,6-migrated products **6a** and **6b** (Figure 2).

Having synthesized, a series of 2-*C*-branched levoglycosan derivatives involving 1,6-transposition reaction, we focused our attention on incorporating the *p*-methoxy benzyl or prenyl group on another oxygen atom, apart from the C6 position. Thus, *p*-methoxy benzyl protected 3-deoxy 3-*C*-branched glycal **29** was synthesized from glycal **28**[19] and subjected to TMSOTf mediated 1,6-transposition reaction. Interestingly, this reaction also proceeded smoothly and gave the expected 2,3-dideoxy carbon-branched bicyclic acetal **30** as a 1:1 mixture of diastereomers in 60% yield (Table 2, entry 1). Extending the methodology to other PMB protected 3-*C*-branched galactal derivative **32**, synthesized

Table 2. Synthesis of 2,3-dideoxy 2- and 3-*C*-branched bicyclic acetal derivatives by 1,5-alkyl transposition reaction.



Entry	3-*C*-Branched alcohol	Protected-3-*C*-branched glycal (%)[a]	2,8-Dioxabicyclo[3.3.1] nonane derivative (%)[a]
1	**28**	**29** (96)	**30a:30b** (60) (1:1)[b,c]
2	**31**	**32** (95)	**33a:33b** (50) (1:1)[b,c]
3	**28**	**34** (95)	**35a:35b** (50) (1:1)[b,c]
4	**31**	**36** (95)	**37a:37b** (50) (1:1)[b,c]
5	**28**	**38** (70)	**39** (80)[d]

[a] Yield refers to pure and isolated products. [b] The diastereomeric ratio was calculated based on the ^{1}H NMR spectra of crude product. [c] The major byproduct was found to be the corresponding 4-(benzyloxy)-3-((benzyloxy)methyl)-2,8-dioxabicyclo[3.3.1]nonane derivative. [d] The stereochemistry at the anomeric position was assigned based on ^{1}H-^{1}H NOESY experiment.

from **31**, also led to the formation of the 1,5-alkyl migrated carbon-branched bicyclic acetal **33** (table 2, entry 2). Further, we proceeded to investigate the generality of this 1,5- alkyl transposition reaction using prenyl protected 3-*C*-branched glycals. Thus, the hydroxyl group in 3-*C*-branched glycals **28** and **31** were treated with prenyl bromide in the presence of NaH in THF to obtain prenyl ether containing 3-*C*-branched glycals **34**

and **36**. Subjecting these glycals to TMSOTf at -78 ºC provided the 2-*C*-prenyl substituted 3-*C*-branched bicyclic acetals **35** and **37**, respectively, as a 1:1 mixture of diastereomers. However, 1,5-alkyl transposition of the *p*-methoxybenzoyl group in glycal derivative **38** was again unsuccessful. Instead, this reaction provided the *C*-disaccharide **39** as a single diastereomer (table 2, entry 5).

Conclusion

In conclusion, we have reported an unprecedented 1,5- and 1,6-alkyl transposition reaction of 3-deoxy glycals. The methodology provides access to the synthesis of various 2-*C*-branched levoglycosan derivatives as well as 2,8-dioxabicyclo[3.3.1]nonane systems. To the best of knowledge, this is the first of its kind in the literature. The application of the developed methodology in total synthesis of natural products[20] and novel sugar derived scaffolds is in progress.

Experimental Section

General method for the 1,6-alkyl migration (exemplified for compounds 5a and 5b): A stirred solution of compound **4** (700 mg, 1.9 mmol) in dry dichloromethane (20 mL) under inert atmosphere was added 4 Å MS and the suspension was cooled to -78 ºC. TMSOTf (34 µL, 0.19 mmol) was added dropwise and continued stirring at the same temperature. After 15 min the reaction was quenched by the addition of Et_3N (~60 µL) and allowed it to come to room temperature. The reaction mixture was filtered through a small pad of Celite and the filter cake was washed with dichloromethane (20 mL). Evaporation of the solvent under reduced pressure followed by column chromatography of the obtained crude product provided the mixture of 2-*C*-branced levoglucosan derivatives **5a** and **5b** (1:1) (666 mg) as a colourless gum in 95% yield. R_f: 0.75 (20% EtOAc/hexanes). **5a:** IR (neat): 2934, 2892, 2835, 1610, 1509 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27 (d, 2H, J = 8.4 Hz), 7.08 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.4 Hz), 5.26 (s, 1H), 4.56-4.58 (m, 1H), 4.50-4.54 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77-3.79 (m, 1H), 3.71-3.73 (m, 1H), 3.35-3.36 (m, 1H), 2.57 (dd, 1H, J = 8.0 Hz, J = 13.6 Hz), 2.39 (dd, 1H, J = 6.8 Hz, J = 13.6 Hz), 2.19-2.27 (m, 1H), 1.74-1.79 (m, 1H), 1.44-1.49 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.19, 157.90, 131.07, 130.23, 129.90, 129.22, 113.79, 113.75, 103.36, 74.58, 72.58, 70.07, 66.41, 55.25, 55.21, 39.12, 37.30, 27.64. **HRMS (ESI)** calcd for $C_{22}H_{26}O_5$+Na^+ 393.1672, found 393.1672. **5b:** $[\alpha]_D^{25}$ -50.4 (*c* 0.63, $CHCl_3$); IR (neat): 2956, 2920, 2853, 1608, 1510 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.8 Hz), 6.91 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 5.37 (s, 1H), 4.61-4.64 (m, 2H), 4.54 (d, 1H, J = 12.0 Hz), 3.83 (s, 3H), 3.80 (s, 3H), 3.75-3.79 (m, 2H), 3.32-3.33 (m, 1H), 2.94 (dd, 1H, J = 7.2 Hz, J = 13.6 Hz), 2.87 (dd, 1H, J = 9.2 Hz, J = 14.0 Hz), 1.90 (dd, 1H, J = 7.6 Hz, J = 15.6 Hz), 1.78-1.84 (m, 1H), 1.67 (d, 1H, J = 14.8 Hz). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.18, 157.84, 132.76, 130.46, 130.16, 129.05, 113.83, 113.74, 104.09, 75.33, 73.17, 70.12, 66.03, 55.28, 55.24, 40.48, 36.40, 23.17. **HRMS (ESI)** calcd for $C_{22}H_{26}O_5$+Na^+ 393.1672, found 393.1671.

Acknowledgements

The authors thank DST-SERB grant (File No. EMR/20l6/007816) for financial support. B.U.R thank UGC-India for Senior Research Fellowship.

Keywords: Carbohydrates • Deoxy-Glycals • Carbocation • Rearrangement • Carbon-branched sugars

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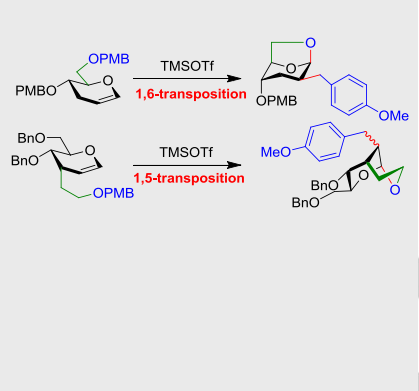
An unprecedented 1,5- or 1,6-alkyl transposition reaction of 3-deoxy glycals led to the formation of various carbon branched bicyclic frameworks.



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Synthesis of Carbon-branched Sugars Involving an Unprecedented 1,5- or 1,6-Alkyl Transposition Reaction